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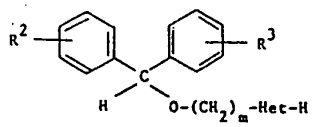
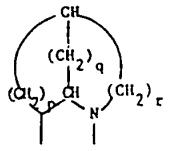
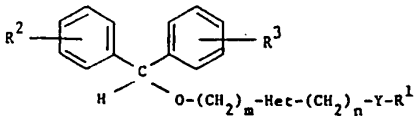


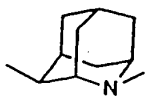
(IB)



(A)



(IA)



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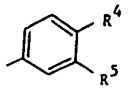
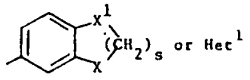


(a)



(b)

(57) Abstract

Muscarinic receptor antagonists, useful especially in the treatment of irritable bowel syndrome, of formula (IA) or (IB) or a pharmaceutically acceptable salt thereof, where R^2 and R^3 are each independently H, halo or C_1-C_4 alkyl; m is 0, 1 or 2; n is 1, 2 or 3; Y is a direct link, O or S; with the proviso that when n is 1, Y is a direct link; Het is a group of formula (A) or (B), where p is 0, 1 or 2, q is 1, 2 or 3, and r is 0, 1, 2 or 3, with the proviso that the sum of p, q and r is at least 3, the N atom of "Het" being attached to the group $(CH_2)_n$ in formula (IA) and to the H atom in formula (IB); and R^1 is a group of formula (a), (b) or Het^1, where R^4 and R^5 are each independently H, C_1-C_4 alkyl, C_1-C_4 alkoxy, $-(CH_2)_tOH$, halo, trifluoromethyl, cyano, $-(CH_2)_tNR^6R^7$, $-CO(C_1$-C_4 alkyl), $-OCO(C_1$-C_4 alkyl), $CH(OH)(C_1$-C_4 alkyl), $-C(OH)(C_1$-C_4 alkyl)$_2$, $-SO_2NH_2$, $-(CH_2)_tCONR^6R^7$ or $-(CH_2)_tCOO(C_1$-C_4 alkyl); R^6 and R^7 are each independently H or C_1-C_4 alkyl; t is 0, 1 or 2; X and X^1 are each independently O or CH_2; s is 1, 2 or 3; and Het^1 is pyridyl, pyrazinyl or thienyl.

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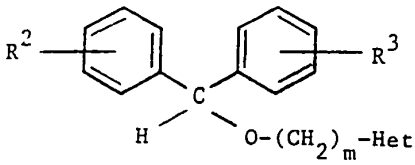
MUSCARINIC RECEPTOR ANTAGONISTS

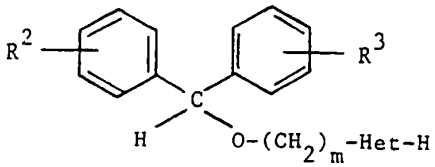
This invention relates to certain azabicyclic compounds which are muscarinic receptor antagonists being selective for smooth muscle muscarinic sites over cardiac muscarinic sites. Thus the compounds are useful in the treatment of diseases associated with altered motility and/or tone of smooth muscle which can, for example, be found in the gut, trachea and bladder. Such diseases include irritable bowel syndrome, diverticular disease, urinary incontinence, oesophageal achalasia and chronic obstructive airways disease.

According to the invention there are provided compounds of the formula:-



--- (IA)

and



--- (IB)

and their pharmaceutically acceptable salts,

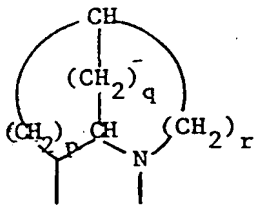
where R^2 and R^3 are each independently H, halo or C_1-C_4 alkyl;

m is 0, 1 or 2;

n is 1, 2 or 3;

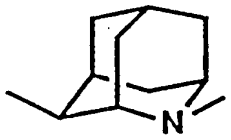
Y is a direct link, O or S; with the proviso that when n is 1, Y is a direct link;

Het is a group of the formula:-



(A)

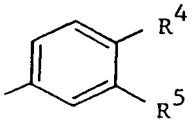
or



(B)

where p is 0, 1 or 2, q is 1, 2 or 3, and r is 0, 1, 2 or 3, with the proviso that the sum of p, q and r is at least 3, the N atom of "Het" being attached to the group $(CH_2)_n$ in formula (IA) and to the H atom in formula (IB);

and R^1 is a group of the formula:-



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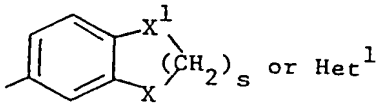


where R^4 and R^5 are each independently H, C_1-C_4 alkyl, C_1-C_4 alkoxy, $-(CH_2)_tOH$, halo, trifluoromethyl, cyano, $-(CH_2)_tNR^6R^7$, $-CO(C_1$-C_4 alkyl), $-OCO(C_1$-C_4 alkyl), $-CH(OH)(C_1$-C_4 alkyl), $-C(OH)(C_1$-C_4 alkyl$)_2$, $-SO_2NH_2$, $-(CH_2)_tCONR^6R^7$ or $-(CH_2)_tCOO(C_1$-C_4 alkyl);

R^6 and R^7 are each independently H or C_1-C_4 alkyl;

t is 0, 1 or 2;

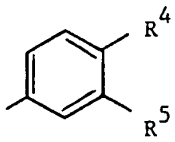
X and X^1 are each independently O or CH_2;

s is 1, 2 or 3;

and Het^1 is pyridyl, pyrazinyl or thienyl.

"Halo" means F, Cl, Br or I. Alkyl and alkoxy groups of 3 or 4 carbon atoms can be straight or branched chain. The preferred alkyl and alkoxy groups are methyl, ethyl, methoxy and ethoxy.

R^1 is preferably a group of the formula:-



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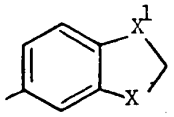
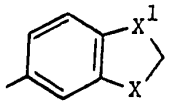


where R^4, R^5, X and X^1 are as defined above.

R^1 is more preferably:-



where X and X^1 are as defined above.

X and X^1 are both most preferably O.

R^2 and R^3 are both preferably H.

m is preferably 0 or 1.

n is preferably 1 or 2.

Y is preferably a direct link.

The sum of p, q and r is preferably 3 or 4.

In "Het", formula (A), preferably:-

(i) p is 0, q is 2 and r is 1,

(ii) p is 1, q is 1 and r is 1,

(iii) p is 1, q is 2 and r is 1.

or (iv) p is 2, q is 2 and r is 0.

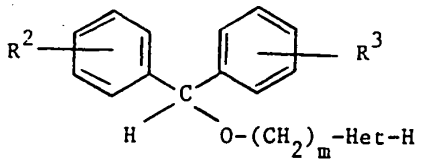
It should be understood that the invention includes all the isomers of the compounds (IA) and (IB), e.g., where applicable, the syn and anti, and exo and endo forms, as well as racemates and separated enantiomers.

The pharmaceutically acceptable salts of the compounds of formula (I) include acid addition salts such as the hydrochloride, hydrobromide, sulphate or bisulphate, phosphate or hydrogen phosphate, acetate, besylate, citrate, fumarate, gluconate, lactate, maleate, mesylate, succinate and tartrate salts. For a more comprehensive list of pharmaceutically acceptable salts see, for example, the Journal of Pharmaceutical Sciences, Vol. 66, No. 1, January 1977, pages 1-19. These salts can be prepared conventionally, e.g. by mixing a solution of the free base and the acid in a suitable solvent, e.g. ethanol, and recovering the acid addition salt either as a precipitate, or by evaporation of the solution.

The compounds of the formula (IA) and (IB) can be prepared by a number of routes, including the following:-

Route A

This route to the compounds (IA) can be illustrated as follows:-



(IB)

+ $Q-(CH_2)_n-Y-R^1 \longrightarrow$ Compounds (IA)

(II)

R^1, R^2, R^3, Y, Het, m and n are as defined for formula (IA) and Q is a leaving group, e.g. Br, Cl, I, C_1-C_4 alkanesulfonyloxy (e.g. methanesulfonyloxy), benzenesulfonyloxy, toluenesulfonyloxy (e.g. p-toluenesulfonyloxy) or trifluoromethanesulfonyloxy. Preferably, Q is Cl, Br, I or methanesulfonyloxy.

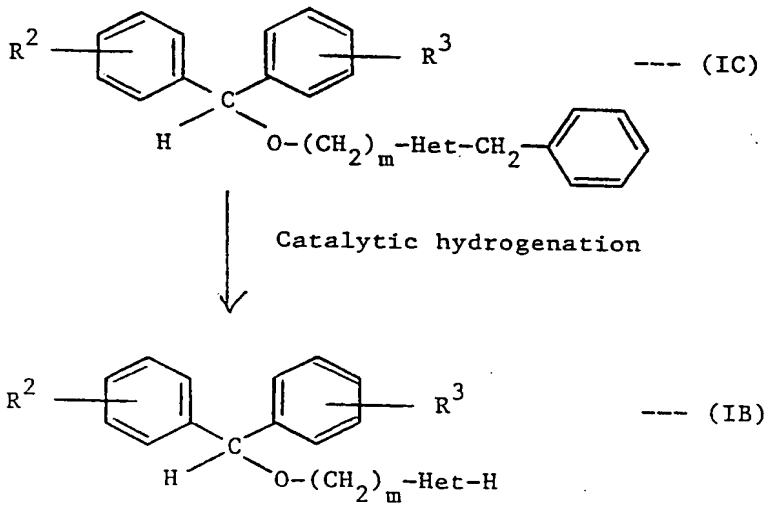
The reaction is preferably carried out in the presence of an acid acceptor such as sodium or potassium carbonate, triethylamine or pyridine, and in a suitable organic solvent, e.g. acetonitrile, at up to the reflux temperature. Reaction temperatures of 60-120°C are generally desirable and it is most convenient to carry out the reaction under reflux. Iodo is often a particularly suitable leaving group but since the starting materials (II) are sometimes most conveniently available as chlorides or bromides the reaction can also be carried out using the compound (II) as a chloride or bromide but in the presence of an iodide such as sodium or potassium iodide. In the preferred technique, the compounds (II) and (III) are refluxed together in acetonitrile in the presence of sodium carbonate and sodium iodide. The product (IA) can be isolated and purified conventionally.

The preparation of the compounds (IB) is described subsequently.

The starting materials of the formula (II) are in general known compounds which can be prepared by conventional techniques. The preparation of any novel starting materials of the formula (II) used in the Examples is however described in the following Preparations section.

Route B

This route to the compounds (IB) can be illustrated as follows:-



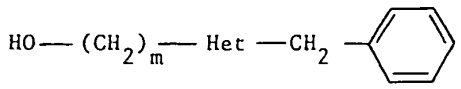
where R^2, R^3, Het and m are as defined for formula (IB).

The hydrogenation can be carried out conventionally, e.g. in ethanol at 40-50°C in the presence of palladium-on-charcoal and optionally acetic acid at a hydrogen pressure of about 50 psi (344.7 kPa).

The starting materials (IC) can be prepared as described in Route C.

Route C

This route to the compound (IC) can be illustrated as follows:-



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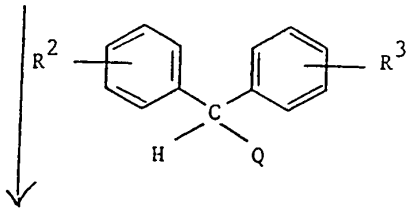


--- (IV)

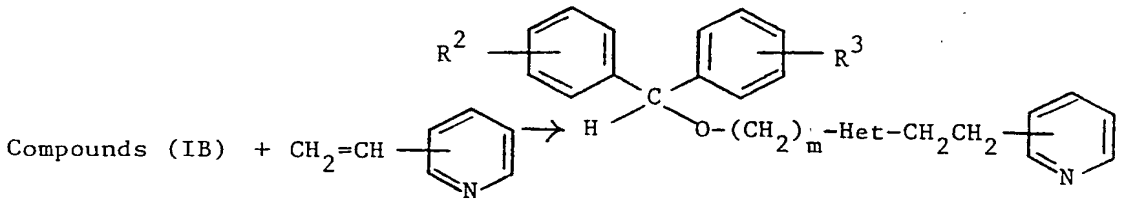
Compounds (IC)

Q is either a leaving group as defined in Route A (preferably Br) or is a hydroxy group. When Q is a leaving group, the reaction is typically carried out by heating the reactants together at 140-150°C. Sometimes the reaction is best carried out in an organic solvent such as xylene under reflux. When Q is OH, the reaction is typically carried out under reflux in an organic solvent such as toluene and in the presence of a dehydrating agent such as p-toluenesulphonic acid.

The compounds (III), if not commercially available, are either known compounds [see e.g. J. Org. Chem., 3822, 39 (1974); J. Org. Chem., 3091, 38 (1973); U.S.-A-4013668; J. Het. Chem., 395, 9 (1972] or are preparable by conventional techniques (see e.g. Preparations 1 to 4).

Route D

This route is useful for preparing compounds in which n is 2, Y is a direct link and R^1 is 2- or 4-pyridyl or pyrazinyl, and can be described as follows:-



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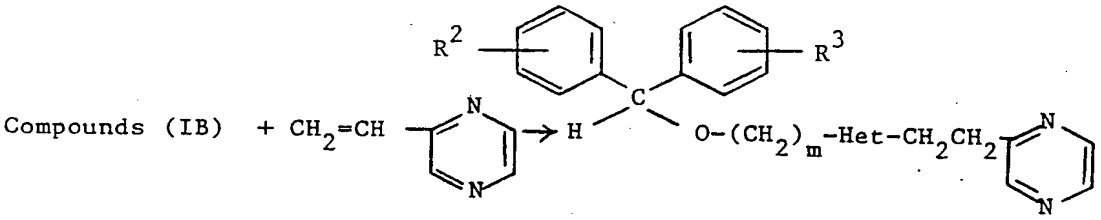


R^2, R^3, m and Het are as defined for formula (I). Clearly the vinyl group must be attached to the 2- or 4-position of the pyridine ring.

The reaction is typically carried out with heating, e.g. at about 60° to 110°C and preferably under reflux, in a suitable organic solvent, e.g. dioxan. In some instances, the use of a basic (preferably a strong base which is soluble in an organic solvent such as N-benzyltrimethylammonium hydroxide ["Triton B"]) or acidic (preferably a C_1-C_4 alkanoic acid) catalyst may be beneficial.

Some of the compounds of the formula (I) in which R^1 is a substituted phenyl group can be converted to other compounds of the formula (I) as follows:-

(a) A $-CO_2(C_1-C_4$ alkyl) substituent on the phenyl group can be selectively reduced to $-CH_2OH$. Lithium aluminium hydride is the most suitable reducing agent. The reaction is typically carried in a suitable organic solvent, e.g. ether, at between 0° and room temperature. It is generally most convenient to use the starting material in the form of its methyl ester.

(b) A hydroxy substituent on the phenyl group can be converted to $-OCO(C_1-C_4$ alkyl) by acylation using a C_1-C_4 alkanoyl chloride or bromide, or an alkanoic anhydride of the formula $(C_1-C_4$ alkyl.CO$)_2O$. The presence of an acid acceptor is preferable. The reaction is typically carried out at about room temperature in a suitable organic solvent, e.g. dioxan.

(c) A $-CO(C_1-C_4$ alkyl) substituent on the phenyl group can be reduced to a substituent of the formula $-CH(OH)(C_1-C_4$ alkyl). A suitable reducing agent is sodium borohydride. The reaction is typically carried out at between 0° and room temperature in a suitable organic solvent, e.g. methanol.

(d) A $-(CH_2)_tCOO(C_1-C_4$ alkyl) substituent, preferably where the alkyl group is methyl, can be converted to $-(CH_2)_tCONR^6R^7$ by reaction with ammonia or the appropriate amine R^6R^7NH. When R^6 and R^7 are both H, the use of aqueous (0.880) ammonia is generally most convenient, although the reaction can be carried out using ammonia in an organic solvent such as methanol or ethanol, or ammonia neat in a bomb. Although in some instances the reaction may proceed at a satisfactory rate at room temperature, heating at up to 120°, preferably 60 to 100°C, is generally necessary. For volatile amines, the reaction is best carried out in a bomb.

(e) A hydroxy substituent can be converted to C_1-C_4 alkoxy firstly by reaction with a base such as potassium carbonate, and secondly by reaction with a C_1-C_4 alkyl iodide or bromide. The reaction is typically carried out in a solvent such as dioxan or acetone, and preferably under reflux.

(f) A hydroxymethyl or hydroxyethyl substituent on the phenyl group can be converted to $-CH_2NR^6R^7$ or $-(CH_2)_2NR^6R^7$ firstly by reaction with thionyl chloride and secondly by reaction with ammonia or the appropriate amine R^6R^7NH. The reaction with thionyl chloride is typically carried out with heating, preferably under reflux, in a solvent such as methylene chloride. The reaction with ammonia or the amine is typically carried out at in a solvent such as ethanol, and heating, e.g. under reflux, may be necessary.

(g) A $-CO(C_1$-C_4 alkyl) substituent can be converted to $-C(OH)(C_1$-C_4 alkyl)$_2$ by reaction with a C_1-C_4 alkyllithium or C_1-C_4 alkylmagnesium bromide, chloride, or iodide (e.g. methyllithium, methylmagnesium bromide, methylmagnesium iodide or methylmagnesium chloride). The reaction is typically carried out in a solvent such as ether at a temperature of from 0°C to room temperature.

and (h) An iodo substituent can be converted to C_1-C_4 alkoxycarbonyl by reaction, typically at about room temperature, with carbon monoxide in a C_1-C_4 alkanol containing a base [e.g. potassium carbonate] and a palladium (II) catalyst [e.g. bis(triphenylphosphine)palladium (II) chloride].

The selectivity of the compounds as muscarinic receptor antagonists can be measured as follows.

Male guinea pigs are sacrificed and the ileum, trachea, bladder and right atrium are removed and suspended in physiological salt solution under a resting tension of 1 g at 32°C aerated with 95% O_2 and 5% CO_2. Contractions of the ileum, bladder and trachea are recorded using an isotonic (ileum) or isometric transducer (bladder and trachea). The frequency of contraction of the spontaneously beating right atrium is derived from isometrically recorded contractions.

Dose-response curves to either acetylcholine (ileum) or carbachol (trachea, bladder and right atrium) are determined using a 1-5 minute contact time for each dose of agonist until the maximum response is achieved. The organ bath is drained and refilled with physiological salt solution containing the lowest dose of the test compound. The test compound is allowed to equilibrate with the tissue for 20 minutes and the agonist dose-response curve is repeated until the maximum response is obtained. The organ bath is drained and refilled with physiological salt solution containing the second concentration of test compound and the above procedure is repeated. Typically four concentrations of the test compound are evaluated on each tissue.

The concentration of the test compound which causes a doubling of the agonist concentration to produce the original response is determined (pA_2 value - Arunlakshana and Schild (1959), Brit. J. Pharmacol., 14, 48-58). Using the above analytical techniques, tissue selectivity for muscarinic receptor antagonists is determined.

Activity against agonist induced bronchoconstriction or gut or bladder contractility in comparison with changes in heart rate is determined in the anaesthetised dog. Oral activity is assessed in the conscious dog determining compound effects on, for example, heart rate, pupil diameter and gut motility.

Compound affinity for other cholinergic sites is assessed in the mouse after either intravenous or intraperitoneal administration. Thus, the dose which causes a doubling of pupil size is determined as well as the dose which inhibits the salivation and tremor responses to intravenous oxotremorine by 50%.

For administration to man in the curative or prophylactic treatment of diseases associated with the altered motility and/or tone of smooth muscle, such as irritable bowel syndrome, diverticular disease, urinary incontinence, oesophageal achalasia and chronic obstructive airways disease, oral dosages of the compounds will generally be in the range of from 3.5 to 350 mg daily for an average adult patient (70 kg). Thus for a typical adult patient, individual tablets or capsules will typically contain from 1 to 250 mg of active compound, in a suitable pharmaceutically acceptable vehicle or carrier for administration singly or in multiple doses, once or several times a day. Dosages for intravenous administration will typically be within the range 0.35 to 35 mg per single dose as required. In practice the physician will determine the actual dosage which will be most suitable for an individual patient and it will vary with the age, weight and response of the particular patient. The above dosages are exemplary of the average case but there can, of course, be

individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention.

For human use, the compounds of the formula (IA) and (IB) can be administered alone, but will generally be administered in admixture with a pharmaceutical carrier selected with regard to the intended route of administration and standard pharmaceutical practice. For example, they may be administered orally in the form of tablets containing such excipients as starch or lactose, or in capsules or ovules either alone or in admixture with excipients, or in the form of elixirs or suspensions containing flavouring or colouring agents. They may be injected parenterally, for example, intravenously, intramuscularly or subcutaneously. For parenteral administration, they are best used in the form of a sterile aqueous solution which may contain other substances, for example, enough salts or glucose to make the solution isotonic with blood.

In a further aspect the invention provides a pharmaceutical composition comprising a compound of the formula (IA) or (IB), or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable diluent or carrier.

The invention also includes a compound of the formula (IA) or (IB) or a pharmaceutically acceptable salt thereof, for use as a medicament, particularly for use in the treatment of irritable bowel syndrome.

The invention further includes the use of a compound of the formula (IA) or (IB), or of a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of

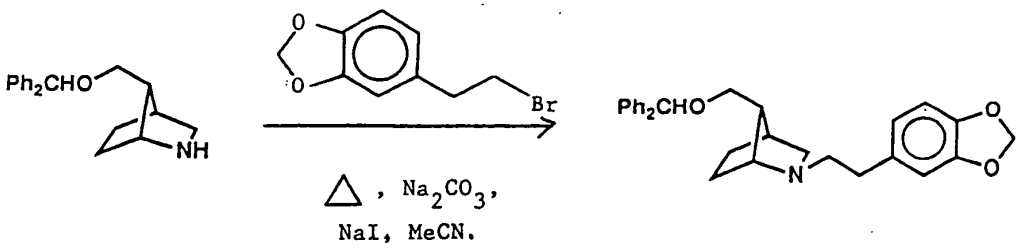
diseases associated with the altered motility and/or tone of smooth muscle, such as irritable bowel syndrome, diverticular disease, urinary incontinence, oesophageal achalasia and chronic obstructive airways disease.

The invention yet further includes a method of treatment of a human being to cure or prevent a disease associated with the altered motility and/or tone of smooth muscle, such as irritable bowel syndrome, which comprises treating said human being an effective amount of a compound of the formula (IA) and (IB), or a pharmaceutically acceptable salt or composition thereof.

The following Examples illustrate the preparation of the compounds of the formula (I):-

EXAMPLE 1

7-anti-(Diphenylmethoxymethyl)-2-(3,4-methylenedioxyphenethyl)-2-azabicyclo[2.2.1]heptane



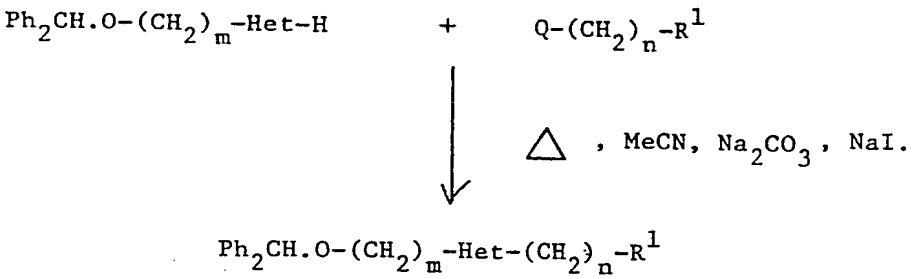
A mixture of 7-anti-diphenylmethoxy-2-azabicyclo-[2.2.1]heptane (0.18 g - see Example 10), 3,4-methylenedioxy-phenethyl bromide (0.23 g - see Preparation 9), sodium carbonate (0.50 g) and sodium iodide (50 mg) in acetonitrile (20 ml) was heated under reflux for 18 hours and diluted with water and ethyl acetate. The layers were separated and the organic layer was washed with water, dried over magnesium sulphate and evaporated. The residue was purified by chromatography on silica using dichloromethane plus 20% ethyl acetate plus 0-5% methanol as the eluant. Appropriate fractions were combined and evaporated to give the title compound (140 mg, 54%) as a colourless oil which was characterised containing 0.25 equivalents of water.

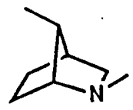
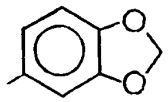
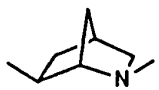
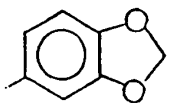
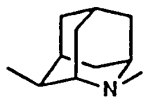
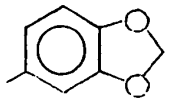
Analysis %:-

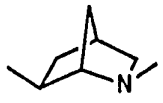
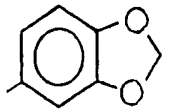
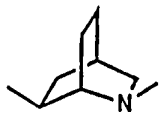
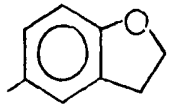
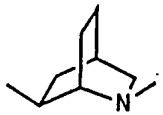
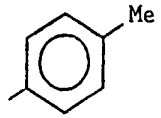
Found:	C,77.9; H,7.1; N,3.2;
$C_{29}H_{31}NO_3.0.25\ H_2O$ requires:	C,78.1; H,7.1; N,3.1.

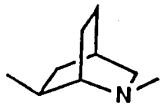
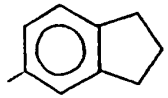
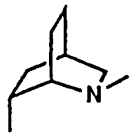
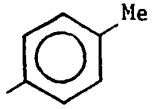
EXAMPLES 2-9

The following compounds were prepared by reacting the appropriate diphenylmethoxy-substituted amine with the appropriate alkylating agent as described in Example 1. The compounds were characterised in the forms indicated.



Example No.	m	Het	n	R^1	Q	Form Characterised	Analysis % (Theoretical in brackets) C	H	N
2	1		1		Cl	Oil	Characterised by its ^{1}H-NMR spectrum. ^{1}H-NMR ($CDCl_3$) δ = 7.18-7.40 (10H, m); 7.13 (1H, s); 7.01 (1H, d, J = 8Hz); 6.78 (1H, d, J = 8Hz); 5.96 (2H, s); 5.32 (1H, s); 3.83 (2H, q, J = 8Hz); 3.65 (1H, broad s); 3.57 (2H, quintet, J = 7Hz); 2.90 (2H, broad s); 2.10-2.60 (3H, m); 1.45-1.70 (3H, m).		
3	0		2		Br	Oil	78.5	6.3	3.3
							(78.7	6.8	3.3)
4	0		2		Br	Oil	79.4	7.1	3.4
							(79.7	7.1	3.0)

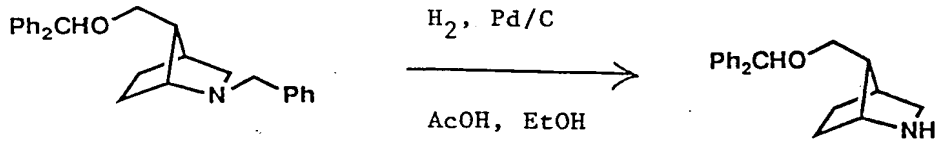
Example No.	m	Het	n	R^1	Q	Form Characterised	Analysis % (Theoretical in brackets) C H N
5	1		2		Br	Oil	Characterised by its ^{1}H-NMR spectrum. ^{1}H-NMR ($CDCl_3$) δ = 7.18-7.40 (10H, m); 6.57-6.78 (3H, m); 5.92 (2H, s); 5.29 (1H, s); 3.44 (1H, broad s); 2.20-3.35 (9H, m); 1.05-1.70 (5H, m).
6	0		2		Br	Oil	81.8 7.5 3.3 (82.0 7.6 3.2)
7	0		2		Br	Oil	84.2 8.1 3.4 (84.6 8.1 3.4)

Example No.	m	Het	n	R^1	Q	Form Characterised	Analysis % (Theoretical in brackets) C	H	N
8	0		2		Br	Oil	85.0 (85.1	8.1 8.1	3.1 3.2)
9	0		2		Br	Oil	Characterised by its ^{1}H-NMR spectrum. ^{1}H-NMR ($CDCl_3$) δ = 7.22-7.50 (10H, m); 7.08 (4H, s); 5.53 (1H, s); 3.64-3.72 (1H, m); 2.63-3.12 (8H, m); 2.37 (3H, s); 1.20-2.08 (7H, m).		

The preparation of the amine starting materials used in the Examples 2-9 is described in Examples 10-15.

EXAMPLE 10

7-anti-(Diphenylmethoxymethyl)-2-azabicyclo[2.2.1]heptane



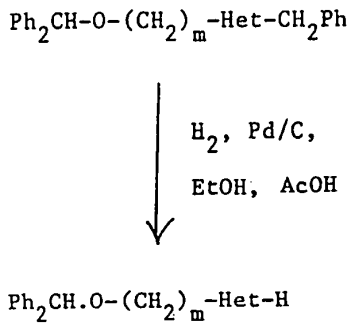
A solution of 2-benzyl-7-anti-(diphenylmethoxymethyl)-2-azabicyclo[2.2.1]heptane (2.30 g - see Example 16) and acetic acid (1.0 ml) in ethanol (200 ml) was stirred at 40-50°C under an atmosphere of hydrogen (50 psi = 344.7 kPa) in the presence of 5% palladium-on-charcoal (250 mg) for 17 hours, filtered and evaporated to give the desired compound as a colourless oil (1.69 g, 96%) which was characterised as containing 0.75 equivalents of water.

Analysis %:-

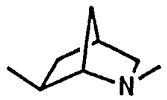
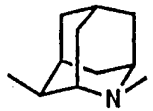
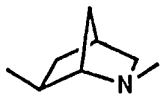
Found:	C,78.6; H,7.8; N,4.4;
$C_{20}H_{23}NO.0.75\ H_2O$ requires:	C,78.3; H,8.0; N,4.6.

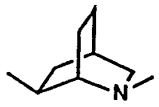
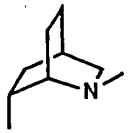
EXAMPLES 11-15

The following compounds were prepared by catalytically hydrogenating the appropriate N-benzyl amine as described in Example 10. The compounds were characterised in the forms indicated.



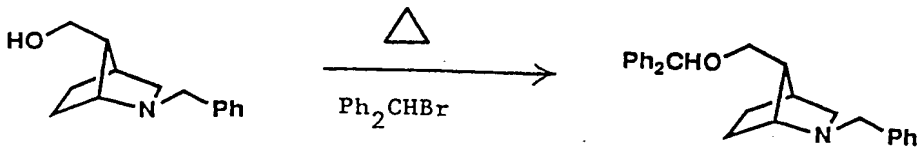
The preparation of the N-benzyl starting materials used in these Examples is described in Examples 22, 23, 24, 17 and 18 respectively.

Example No.	m		Form Characterised	Analysis % (Theoretical in brackets) C	H	N
11	0		oil, 0.25 equivalents of water	80.4 (80.4	7.7 7.6	4.8 4.9)
12	0		oil, hemihydrate	80.0 (80.0	7.8 7.9	3.9 4.2)
13	1		oil	Characterised by its ^{1}H-NMR spectrum ^{1}H-NMR ($CDCl_3$) δ = 7.15-7.40 (10H, m); 5.29 (1H, s); 3.57 (1H, s); 2.04-3.30 (6H, m); 0.75-1.60 (5H, m).		

Example No.	m		Form Characterised	Analysis % (Theoretical in brackets) C	H	N
14	0		oil	81.1 (81.9)	7.8 7.9	4.8 4.8)
15	0		oil	Characterised by its ^{1}H-NMR spectrum. ^{1}H-NMR ($CDCl_3$) δ = 7.18-7.50 (10H, m); 5.52 (1H, s); 3.64 (1H, d, J = 8Hz); 2.90-3.30 (4H, m); 1.20-2.30 (7H, m).		

EXAMPLE 16

2-Benzyl-7-anti-(diphenylmethoxymethyl)-2-azabicyclo[2.2.1]heptane



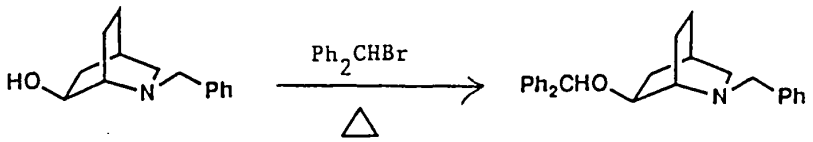
A mixture of 2-benzyl-2-azabicyclo[2.2.1]heptane-7-anti-methanol (4.34 g- commercially available) and bromodiphenylmethane (4.94 g) was heated at 140-150°C for 1 hour and dissolved in ethyl acetate (200 ml). The resulting solution was washed with 5% aqueous sodium carbonate solution, dried over magnesium sulphate and evaporated. The residue was chromatographed on silica using dichloromethane plus 0-10% ethyl acetate followed by dichloromethane plus 1-10% methanol as eluant. Appropriate fractions were combined and evaporated to give the desired compound as a colourless oil (4.90 g, 64%) which was characterised as a hemihydrate.

Analysis %:-

Found:	C,83.1; H,7.5; N,3.7;
$C_{27}H_{29}NO.0.5H_2O$ requires:	C,82.7; H,7.6; N,3.6.

EXAMPLE 17

2-Benzyl-6-exo-diphenylmethoxy-2-azabicyclo[2.2.2]octane



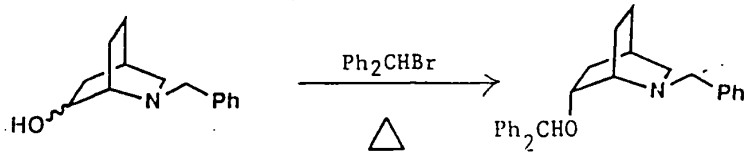
The title compound was prepared as described in Example 16 but using 2-benzyl-2-azabicyclo[2.2.2]octan-6-exo-ol (see U.S.-A-4013668) instead of 2-benzyl-2-azabicyclo[2.2.1]heptane-7-anti-methanol. The title compound was obtained as a colourless oil (3.39 g, 86%).

Analysis %:-

Found:	C,84.4; H,7.5; N,3.6;
$C_{27}H_{29}NO$ requires:	C,84.5; H,7.6; N,3.6.

EXAMPLE 18

2-Benzyl-6-endo-diphenylmethoxy-2-azabicyclo[2.2.2]octane



exo-/endo-
mixture (1.6:1)

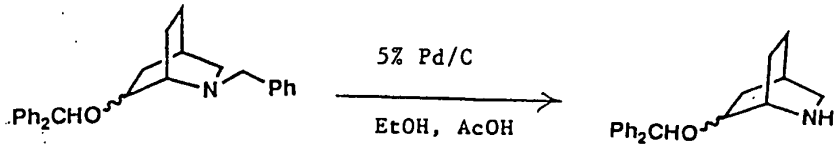
A mixture of 2-benzyl-2-azabicyclo[2.2.2]octan-6-exo-ol and 2-benzyl-2-azabicyclo[2.2.2]octan-6-endo-ol (940 mg; ratio 1.6:1 by ^{1}H-NMR - see Preparation 3) and bromodiphenylmethane (1.05 g) was heated at 150°C for 1.5 hours and dissolved in dichloromethane. The resulting solution was washed with 5% aqueous sodium carbonate solution; dried over sodium sulphate and evaporated. The residue was purified by chromatography on silica using dichloromethane plus 0-4% saturated methanolic ammonia solution as eluant. Appropriate fractions were combined and evaporated to give the desired compound as a colourless oil (250 mg, 16%) which was characterised by its ^{1}H-NMR spectrum.

^{1}H-NMR ($CDCl_3$) δ = 7.20-7.55 (15H, m); 5.45 (1H, s); 3.60-4.04 (3H, m); 3.12 (1H, d, J = 6Hz); 2.93 (1H, broad s); 2.65 (1H, broad s); 1.18-2.14 (7H, m).

Fractions from the above chromatography which contained the above 6-endo-product contaminated with the corresponding 6-exo-isomer were also combined and evaporated to give a colourless oil (0.82 g) which was shown by ^{1}H-NMR to consist of 2-benzyl-6- exo-diphenylmethoxy-2-azabicyclo[2.2.2]octane and 2-benzyl-6- endo-diphenylmethoxy-2-azabicyclo[2.2.2]octane in an approximate ratio of 1:1. A portion of this oil was used in Example 19.

EXAMPLE 19

6-exo-Diphenylmethoxy-2-azabicyclo[2.2.2]octane and 6-endo-diphenylmethoxy-2-azabicyclo[2.2.2]octane (1:1)



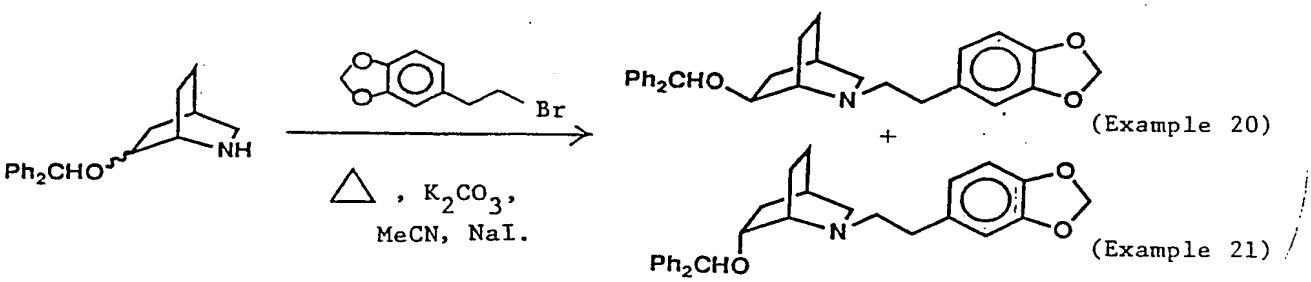
exo-/endo-
(1:1)

exo-/endo-
(1:1)

The mixture of title compounds was prepared as described in Example 10 but using 2-benzyl-6-exo-diphenylmethoxy-2-azabicyclo[2.2.2]octane and 2-benzyl-6-endo-diphenylmethoxy-2-azabicyclo[2.2.2]octane (ratio 1:1 - see Example 18) instead of 2-benzyl-7-anti-(diphenylmethoxymethyl)-2-azabicyclo[2.2.1]-heptane. The mixture of title compounds was obtained as a colourless oil (540 mg, 92%) which was shown by ^{1}H-NMR to be a mixture of the 6-exo- and 6-endo-isomers in an approximate ratio of 1:1 and which was used directly in the preparation of Examples 20 and 21.

EXAMPLES 20 and 21

6-exo-Diphenylmethoxy-2-(3,4-methylenedioxyphenethyl)-2-azabicyclo[2.2.2]octane hemihydrate and 6-endo-diphenylmethoxy-2-(3,4-methylenedioxyphenethyl)-2-azabicyclo[2.2.2]octane hydrate



The title compounds were prepared as described in Example 1 by reacting a mixture of 6-exo-diphenylmethoxy-2-azabicyclo-[2.2.2]octane and 6-endo-diphenylmethoxy-2-azabicyclo[2.2.2]octane (ratio = 1:1, see Example 19) with 3,4-methylenedioxyphenethyl bromide. Work-up as described in Example 1 followed by separation of the residue by chromatography on silica using hexane: 2-propanol:saturated aqueous ammonia (96:4:1) as eluant afforded the title 6-exo- and 6-endo compounds.

Example 20 (exo-isomer)

Analysis %:-

Found: C,77.2; H,7.4; N,3.0;

$C_{29}H_{31}NO_3.\frac{1}{2}H_2O$: C,77.3; H,7.2; N,3.1.

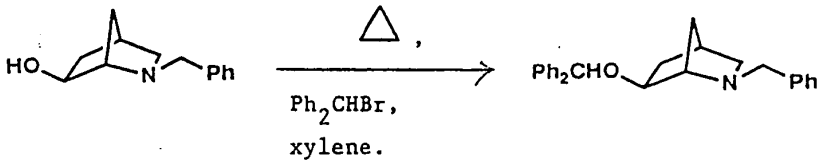
Example 21 (endo-isomer)

Analysis %:-

Found:	C,75.4; H,7.3; N,2.9;
Calculated for $C_{29}H_{31}NO_3.H_2O$:	C,75.8; H,7.2; N,3.0.

EXAMPLE 22

2-Benzyl-6-exo-diphenylmethoxy-2-azabicyclo[2.2.1]heptane hydrobromide



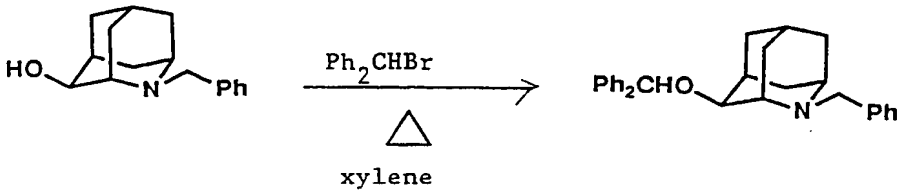
A mixture of 2-benzyl-2-azabicyclo[2.2.1]heptan-6-exo-ol (0.61 g - see Preparation 1 and J. Het. Chem., 395, 9, [1972]) and bromodiphenylmethane (1.48 g) in xylene (10 ml) was heated under reflux for 2 hours, diluted with ethyl acetate, washed with water, dried over sodium sulphate and evaporated. The residue was purified by chromatography on silica using dichloromethane plus 20% ethyl acetate plus 0-5% methanol as the eluant. Appropriate fractions were combined and evaporated to give the desired product as a colourless oil (0.88 g, 65%).

Analysis %:-

Found:	C,71.1; H,6.5; N,3.2;
$C_{26}H_{27}NO.HBr$ requires:	C,69.3; H,6.2; N,3.1.

EXAMPLE 23

2-Benzyl-6-exo-diphenylmethoxy-2-azaadamantane hydrobromide



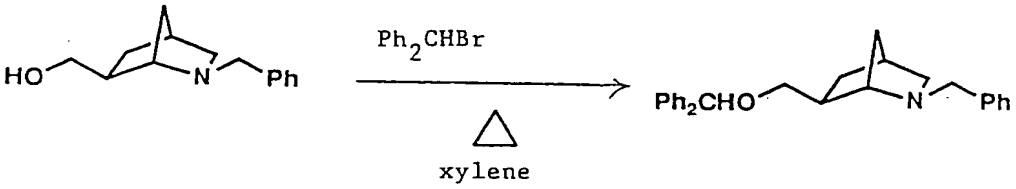
This was prepared as described in Example 22 using 2-benzyl-2-azaadamantan-6-exo-ol (see J. Org. Chem., 3822, 39, [1974] and 3091, 38, [1973]) instead of 2-benzyl-2-azabicyclo-[2.2.1]heptan-6-exo-ol. The title compound was obtained as a colourless foam (0.39 g, 27%).

Analysis %:-

Found:	C,70.9; H,6.9; N,2.9;
$C_{29}H_{31}NO.HBr$ requires:	C,71.0; H,6.5; N,2.9.

EXAMPLE 24

2-Benzyl-6-exo-(diphenylmethoxymethyl)-2-azabicyclo[2.2.1]heptane

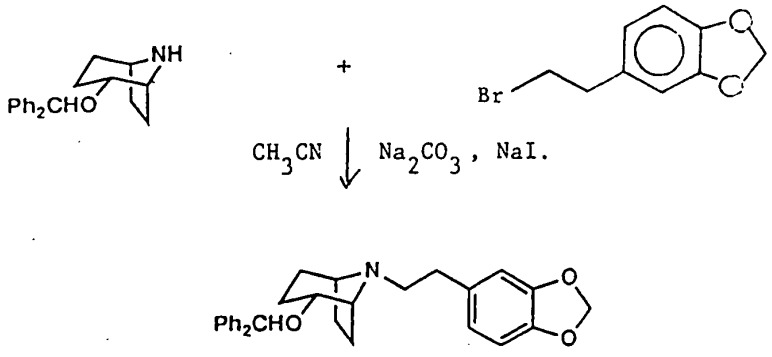


A solution of 2-benzyl-2-azabicyclo[2.2.1]heptane-6-exo-methanol (260 mg - see Preparation 2 but also commercially available) and bromodiphenylmethane (0.49 g) in xylene (20 ml) was heated under reflux for 3 hours, allowed to cool to room temperature, diluted with ethyl acetate, washed with 10% aqueous sodium carbonate solution, dried over sodium sulphate and evaporated. The residue was purified by chromatography on silica using dichloromethane plus 0-20% ethyl acetate followed by dichloromethane plus 20% ethyl acetate plus 2-5% methanol as the eluant. Appropriate fractions were combined and evaporated to give the desired compound as a colourless foam (270 mg, 59%) which was characterised by its ^{1}H-NMR spectrum.

^{1}H-NMR ($CDCl_3$) δ = 7.09-7.74 (15 H, m); 5.23 (1H, s); 3.98 (2H, broad s); 3.60 (1H, broad s); 3.26 (1H, dd, J = 10 and 3Hz); 3.10 (2H, t, J = 10Hz); 2.77 (1H, broad s); 2.49 (1H, broad s); 1.19-1.95 (5H, m).

EXAMPLE 25

2- α-Diphenylmethoxy-8-(3,4-methylenedioxyphenethyl)-8-azabicyclo[3.2.1]octane



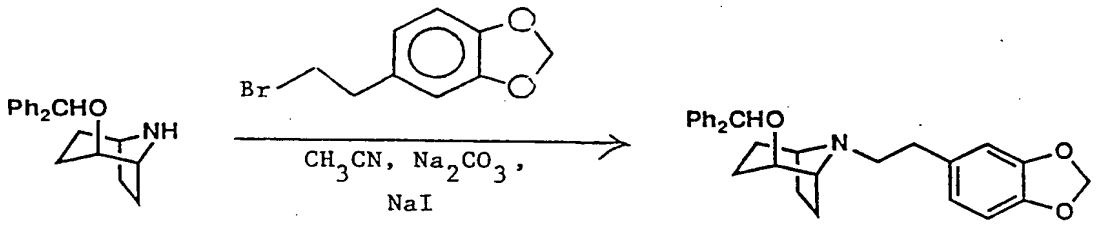
The title compound was prepared as described in Example 1 but using 2- α-diphenylmethoxy-8-azabicyclo[3.2.1]octane (see Example 27) instead of 7-anti-diphenylmethoxy-2-azabicyclo-[2.2.1]heptane. The title compound was obtained as a colourless oil (27 mg, 58%) which was characterised as containing 0.25 equivalents of water.

Analysis %:-

Found:	C,78.0; H,7.0; N,3.2;
$C_{29}H_{31}NO_3.0.25\ H_2O$ requires:	C,78.1; H,7.1; N,3.1.

EXAMPLE 26

2- β-Diphenylmethoxy-8-(3,4-methylenedioxyphenethyl)-8-azabicyclo[3.2.1]octane



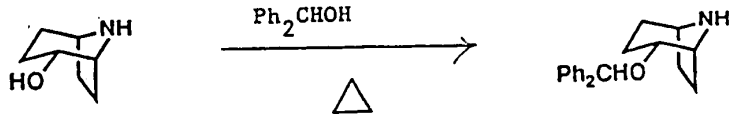
The title compound was prepared as described in Example 1 but using 2- β -diphenylmethoxy-8-azabicyclo[3.2.1]octane (see Example 28) instead of 7-anti-diphenylmethoxy-2-azabicyclo[2.2.1]heptane. The title compound was obtained as a colourless oil (85 mg, 54%) which was characterised as a hemihydrate.

Analysis %:-

Found:	C,77.2; H,6.9; H,3.1;
$C_{29}H_{31}NO_3.0.5\ H_2O$ requires:	C,77.1; H,7.2; N,3.1.

EXAMPLE 27

2-α-Diphenylmethoxy-8-azabicyclo[3.2.1]octane



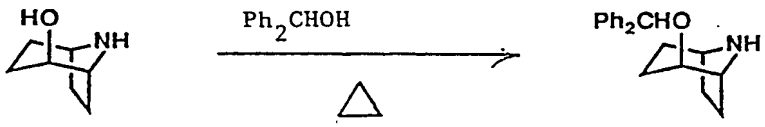
A mixture of 2-α-hydroxy-8-azabicyclo[3.2.1]octane (123 mg - see Preparation 10), para-toluenesulphonic acid monohydrate (237 mg) and benzhydrol (248 mg) in toluene (5 ml) was heated under reflux using a Dean-Stark apparatus for 4 hours. The mixture was partitioned between 2M aqueous sodium hydroxide solution and ether and the organic layer was dried over sodium sulphate and evaporated. The residue was purified by chromatography on silica using dichloromethane plus 0-10% methanol as eluant. Appropriate fractions were combined and evaporated to give the title compound as a colourless oil (51 mg, 17%) which was characterised as a hydrate.

Analysis %:-

Found:	C,76.5; H,7.5; N,4.5;
$C_{20}H_{23}NO.H_2O$ requires:	C,77.1; H,8.1; N,4.5.

EXAMPLE 28

2-β-Diphenylmethoxy-8-azabicyclo[3.2.1]octane



The title compound was prepared as described in Example 27 but using 2-β-hydroxy-8-azabicyclo[3.2.1]octane (see Preparation 11) instead of 2-α-hydroxy-8-azabicyclo[3.2.1]octane. The title compound was obtained as a colourless oil (118 mg, 55%) which was characterised containing 1.33 equivalents of water.

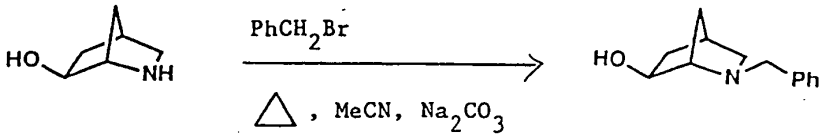
Analysis %:-

Found:	C,75.7; H,7.6; N,4.4;
$C_{20}H_{23}NO.1.33\ H_2O$ requires:	C,75.7; H,8.1; N,4.4.

The following Preparations illustrate the preparation of certain starting materials used in the Examples:-

Preparation 1

2-Benzyl-2-azabicyclo[2.2.1]heptan-6-exo-ol [see also J. Het. Chem., 1972, 9(2), 395].



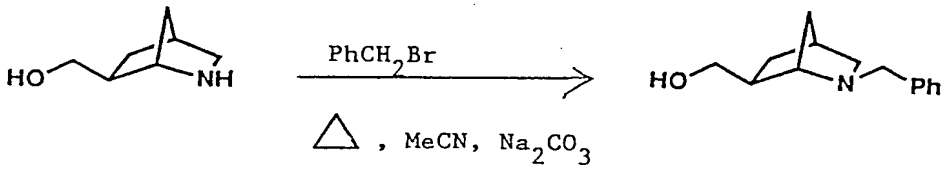
A mixture of 2-azabicyclo[2.2.1]heptan-6-exo-ol (0.75 g - commercially available), benzyl bromide (0.68 g), sodium carbonate (0.50 g) and sodium iodide (50 mg) in acetonitrile (20 ml) was heated under reflux for 16 hours, diluted with ethyl acetate, washed with water, dried over sodium sulphate and evaporated to give the desired compound as a colourless oil, 0.67 g (94%), which was characterised as containing 0.25 equivalents of water.

Analysis %:-

Found:	C,75.4; H,8.3; N,6.7;
$C_{13}H_{17}NO.0.25\ H_2O$ requires:	C,75.2; H,8.4; N,6.7.

Preparation 2

2-Benzyl-2-azabicyclo[2.2.1]heptane-6-exo-methanol

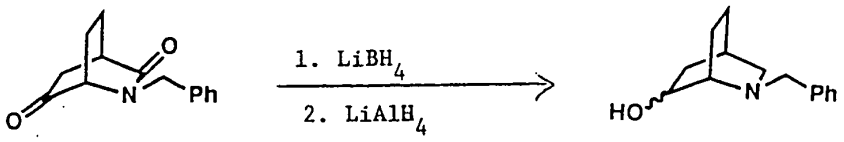


This was prepared as described in Preparation 1 using 2-azabicyclo[2.2.1]heptane-6-exo-methanol (commercially available) instead of 2-azabicyclo[2.2.1]heptan-6-exo-ol. The title compound was obtained as a colourless oil (0.32 g, 55%) which was characterised by its ^{1}H-NMR spectrum.

^{1}H-NMR ($CDCl_3$) δ = 7.15-7.41 (5H, m); 3.63 (2H, AB, J = 15Hz); 3.33-3.48 (2H, m); 3.20 (1H, s); 2.68-2.78 (1H, m); 2.14-2.40 (3H, m); 1.46-1.66 (3H, m); 1.27 (1H, d, J = 8Hz); 1.00-1.17 (1H, m).

Preparation 3

2-Benzyl-2-azabicyclo[2.2.2]octan-6-exo-ol and 2-benzyl-2-azabicyclo[2.2.2]octan-6-endo-ol (ratio 1.6:1)



exo-/endo-

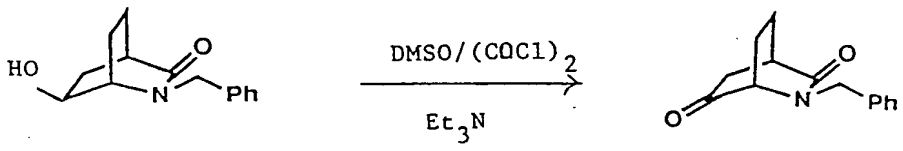
(1.6:1)

Lithium borohydride (1.65 g) was added portionwise over 30 minutes to a solution of 2-benzyl-3,6-dioxo-2-azabicyclo-[2.2.2]octane (1.70 g - see Preparation 4) in dioxane (125 ml) and the mixture was stirred at room temperature for 17 hours and evaporated. The residue was partitioned between dichloromethane and 5% aqueous sodium carbonate solution and the organic layer was washed with water, dried over sodium sulphate and evaporated. The residue was dissolved in tetrahydrofuran (25 ml) and the solution was added dropwise over 30 minutes to a stirred, ice-cooled suspension of lithium aluminium hydride in tetrahydrofuran (75 ml). The mixture was stirred at room temperature for 72 hours, cooled in ice-water, quenched by the cautious dropwise sequential addition of water (1.14 g) in tetrahydrofuran (10 ml), 15% aqueous sodium hydroxide solution (1.14 g) and water (3.42 g) and

filtered. The filtrate was evaporated and the residue was dissolved in dichloromethane, washed with 5% aqueous sodium carbonate solution, dried over sodium sulphate and evaporated. The residue was purified by chromatography on silica using hexane:ethyl acetate:diethylamine (90:10:5) as the eluant. Appropriate fractions were combined and evaporated to give the desired compound as a colourless oil (940 mg, 59%) which was shown by ^{1}H-NMR to consist of a mixture of the <u>exo</u>- and <u>endo</u>-isomers in the ratio 1.6:1. This material was used directly in the preparation of Example 18.

Preparation 4

<u>2-Benzyl-3,6-dioxo-2-azabicyclo[2.2.2]octane</u>

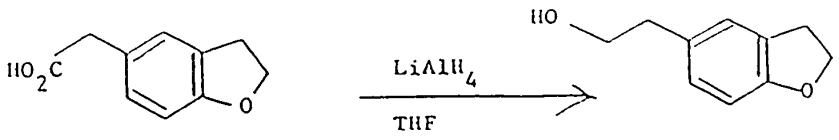


<u>exo</u>-isomer

A solution of dimethyl sulphoxide (2.34 g) in dichloromethane (5 ml) was added to a cooled (-60°C) solution of oxalyl chloride (1.78 g) in dichloromethane (5 ml) and after 2 minutes the mixture was treated with a solution of 2-benzyl-2-azabicyclo-[2.2.2]octan-3-one (2.31 g - commercially available) in dichloromethane (10 ml), stirred at -60°C for 30 minutes, treated with triethylamine (5.05 g), allowed to warm up to room temperature, quenched with water and extracted into dichloromethane. The dichloromethane extracts were dried over sodium sulphate and evaporated. The residue was purified by chromatography on silica using hexane plus 50% ethyl acetate as eluant. Appropriate fractions were combined and evaporated to give the desired compound (2.10 g, 92%) as a colourless oil which was used directly in Preparation 3 without characterisation or further purification.

Preparation 5

5-(2-Hydroxyethyl)-2,3-dihydrobenzofuran

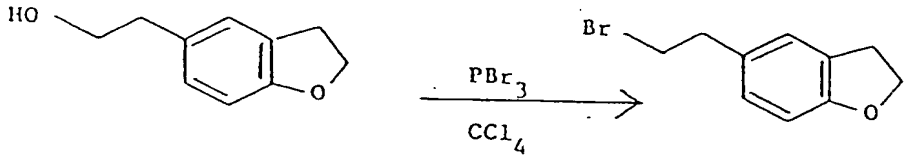


A solution of (2,3-dihydrobenzofuran-5-yl)acetic acid (4.9 g - see EP-A-132130) in anhydrous tetrahydrofuran (50 ml) was added dropwise over 10 minutes to a stirred suspension of lithium aluminium hydride (1.57 g) in anhydrous tetrahydrofuran (50 ml) at 0°C. The mixture was allowed to warm to room temperature and stirred for 1 hour. Water (1.5 ml) was cautiously added dropwise followed by 10% aqueous sodium hydroxide solution (1.5 ml) and water (4.5 ml). The mixture was filtered and the inorganic salts washed with ethyl acetate. The filtrate and washings were combined and evaporated to give the title compound as an oil, yield 3.3 g.

^{1}H-NMR ($CDCl_3$) δ = 7.10 (s, 1H); 7.00 (d, 1H); 6.75 (m, 1H); 4.65-4.55 (m, 2H); 3.90-3.75 (m, 2H); 3.30-3.15 (m, 2H); 2.90-2.80 (m, 2H); 1.85-1.75 (brs, 1H) ppm.

Preparation 6

5-(2-Bromoethyl)-2,3-dihydrobenzofuran

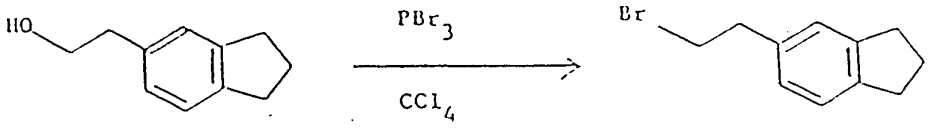


Phosphorus tribromide (0.37 g) was added to a solution of 5-(2-hydroxyethyl)-2,3-dihydrobenzofuran (0.612 g) (see Preparation 5) in carbon tetrachloride (3 ml) and the mixture was heated under reflux for 3 hours. On cooling to room temperature, the mixture was partitioned between 10% aqueous sodium carbonate solution (20 ml) and dichloromethane (20 ml). The layers were separated and the aqueous layer was extracted twice with dichloromethane. The combined dichloromethane extracts were dried over magnesium sulphate and evaporated to give the title compound as an oil which crystallised on standing, yield 0.584 g, m.p. 60-62°C.

^{1}H-NMR ($CDCl_3$) δ = 7.10 (s, 1H); 7.00-6.95 (d, 1H); 6.80-6.70 (d, 1H); 4.65-4.55 (t, 2H); 3.60-3.50 (t, 2H); 3.25-3.15 (t, 2H); 3.15-3.10 (t, 2H) ppm.

Preparation 7

5-(2-Bromoethyl)indane

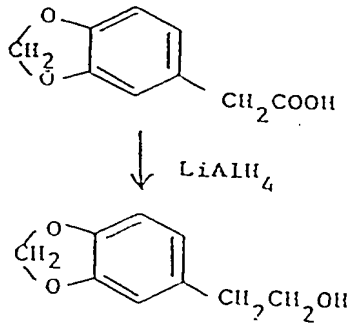


Phosphorus tribromide (3.5 ml) was added dropwise to a solution of 5-(2-hydroxyethyl)indane (14.0 g) (FR-A-2139628) in carbon tetrachloride (100 ml). The mixture was stirred at room temperature for 0.5 hour and then heated under reflux for 2 hours. Ice (100 g) was added and the mixture partitioned between dichloromethane and 10% aqueous sodium carbonate solution. The layers were separated and the aqueous layer extracted twice with dichloromethane. The combined dichloromethane extracts were dried ($MgSO_4$) and evaporated to give an oil which was purified by column chromatography on silica using dichloromethane as the eluant. Appropriate fractions were combined and concentrated in vacuo to give the title compound as a colourless oil, yield 10.5 g.

^{1}H-NMR ($CDCl_3$) δ = 7.30-7.00 (m, 3H); 3.60 (m, 2H); 3.20 (m, 2H); 3.00-2.85 (m, 4H); 2.20-2.05 (m, 2H) ppm.

Preparation 8

3,4-Methylenedioxyphenethyl alcohol

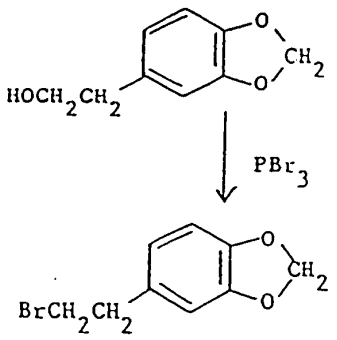


3,4-Methylenedioxyphenylacetic acid (18.0 g) was added portionwise over 30 minutes to a stirred, ice-cooled suspension of lithium aluminium hydride (4.0 g) in ether (400 ml) and the mixture was stirred at room temperature for two hours, quenched by the cautious addition of saturated aqueous ammonium chloride solution and filtered. The filtrate was washed with 10% aqueous sodium carbonate solution, dried over magnesium sulphate and evaporated to give the title compound as a pale yellow oil (15.01 g, 90%) which was characterised by its ^{1}H-NMR spectrum.

^{1}H NMR ($CDCl_3$) δ = 6.69-6.83 (3H, m); 5.98 (2H, s); 3.82 (2H, dt, J = 7 and 6Hz); 2.81 (2H, t, J = 7Hz) and 1.44 (1H, t, J = 6Hz, exchangeable with D_2O).

Preparation 9

3,4-Methylenedioxyphenethyl bromide

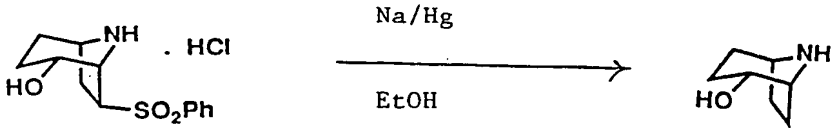


A solution of phosphorus tribromide (8.1 g) in carbon tetrachloride (50 ml) was added dropwise over 30 minutes to a stirred solution of 3,4-methylenedioxyphenethyl alcohol (15.0 g) (see Preparation 8) in carbon tetrachloride (200 ml) and the mixture was heated under reflux for 3 hours, washed sequentially with water (twice), 5M aqueous sodium hydroxide solution and water, dried over magnesium sulphate and evaporated. The residue was purified by chromatography on silica (100 g) using carbon tetrachloride as the eluant. Appropriate fractions were combined and evaporated to give the title compound as a pale yellow oil (8.3 g, 40%) which was characterised by its ^{1}H-NMR spectrum.

^{1}H-NMR ($CDCl_3$) δ = 6.80 (1H, d, J = 8Hz), 6.75 (1H, s); 6.71 (1H, d, J = 8Hz); 6.00 (2H, s); 3.56 (2H, t, J = 7Hz) and 3.13 (2H, t, J = 7Hz).

Preparation 10

2 α-Hydroxy-8-azabicyclo[3.2.1]octane



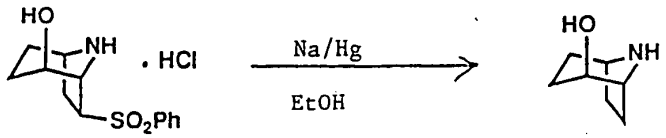
A mixture of 2 ∝-hydroxy-7-syn-phenylsulphonyl-8-azabicyclo-[3.2.1]octane hydrochloride (534 mg) (see Preparation 12) and 5% sodium amalgam (10 g) in ethanol (40 ml) was heated under reflux for 16 hours, filtered and evaporated. The residue was purified by chromatography on silica using dichloromethane plus 20% methanol plus 5% concentrated aqueous ammonia solution as eluant. Appropriate fractions were combined and evaporated to give the title compound (106 mg, 42%) as a colourless oil which was characterised containing 0.25 equivalents of water.

Analysis %:-

Found:	C,64.3; H,9.9; N,10.4;
$C_7H_{13}NO.0.25\ H_2O$ requires:	C,63.8; H,10.3; N,10.6.

Preparation 11

2β-Hydroxy-8-azabicyclo[3.2.1]octane



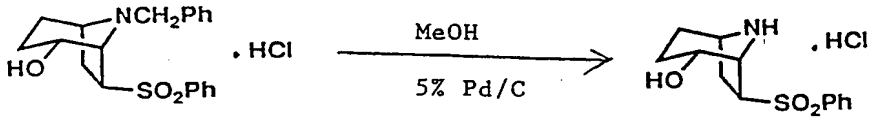
The title compound was prepared as described in Preparation 10 but using 2β-hydroxy-7-syn-phenylsulphonyl-8-azabicyclo-[3.2.1]octane hydrochloride (see Preparation 13) instead of 2∝-hydroxy-7-syn-phenylsulphonyl-8-azabicyclo[3.2.1]octane

hydrochloride. The title compound was obtained as a brown gum (101 mg, 40%) which was characterised by its ^{1}H-NMR spectrum.

^{1}H-NMR ($CDCl_3$) δ = 3.53 (1H, s), 3.32-3.48 (2H, m); 2.87 (2H, s); 1.22-1.96 (8H, m).

Preparation 12

2 α-Hydroxy-7-syn-phenylsulphonyl-8-azabicyclo[3.2.1]octane hydrochloride



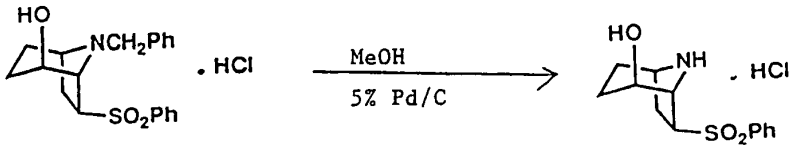
A solution of 8-benzyl-2 α-hydroxy-7-syn-phenylsulphonyl-8-azabicyclo[3.2.1]octane hydrochloride (28.4 g) (Tet. Lett. 1990, 27, 3879; see also Chem. Lett. 1989, 593 for a related synthetic procedure) in methanol (284 ml) was stirred at room temeprature under an atmosphere of hydrogen (60 psi = 413.6 kPa) in the presence of 5% palladium-on-charcoal (2.5 g) for 2 hours, filtered and evaporated. The residue was crystallised from 95% ethanol to give the title compound (19.7 g, 90%) as a colourless solid, m.p. 273°C.

Analysis %:-

Found:	C,57.5; H,6.0; N,4.5;
$C_{13}H_{17}NO_3S.HCl$ requires:	C,57.4; H,6.0; N,4.6.

Preparation 13

2β-Hydroxy-7-syn-phenylsulphonyl-8-azabicyclo[3.2.1]octane hydrochloride



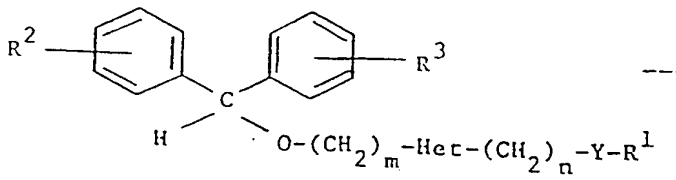
The title compound was prepared as described in Preparation 12 but using 8-benzyl-2β-hydroxy-7-syn-phenylsulphonyl-8-azabicyclo[3.2.1]octane hydrochloride (Tet. Lett. 1990, 27, 3879; see also Chem. Lett. 1989, 593 for a related synthetic procedure) instead of 8-benzyl-2α-hydroxy-7-syn-phenylsulphonyl-8-azabicyclo[3.2.1]octane hydrochloride. The title compound was obtained as a colourless solid (52.9 g, 81%), m.p. 307°C.

Analysis %:-

Found:	C,51.4; H,5.9; N,4.5;
$C_{13}H_{17}NO_3S.HCl$ requires:	C,51.4; H,6.0; N,4.6.

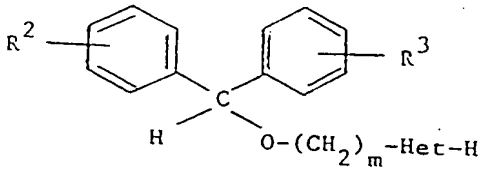
CLAIMS

1. A compound of the formula:-



--- (IA)

or



--- (IB)

or a pharmaceutically acceptable salt thereof,

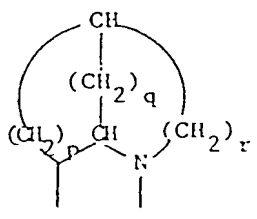
where R^2 and R^3 are each independently H, halo or C_1-C_4 alkyl;

m is 0, 1 or 2;

n is 1, 2 or 3;

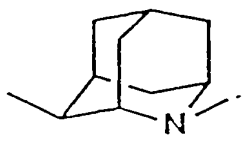
Y is a direct link, O or S; with the proviso that when n is 1, Y is a direct link;

Het is a group of the formula:-



(A)

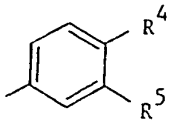
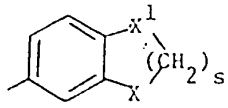
or



(B)

where p is 0, 1 or 2, q is 1, 2 or 3, and r is 0, 1, 2 or 3, with the proviso that the sum of p, q and r is at least 3, the N atom of "Het" being attached to the group $(CH_2)_n$ in formula (IA) and to the H atom in formula (IB);

and R^1 is a group of the formula:-


,

or Het^1

where R^4 and R^5 are each independently H, C_1-C_4 alkyl, C_1-C_4 alkoxy, $-(CH_2)_tOH$, halo, trifluoromethyl, cyano, $-(CH_2)_tNR^6R^7$, $-CO(C_1$-C_4 alkyl), $-OCO(C_1$-C_4 alkyl), $-CH(OH)(C_1$-C_4 alkyl), $-C(OH)(C_1$-C_4 alkyl$)_2$, $-SO_2NH_2$, $-(CH_2)_tCONR^6R^7$ or $-(CH_2)_tCOO(C_1$-C_4 alkyl);

R^6 and R^7 are each independently H or C_1-C_4 alkyl;

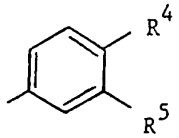
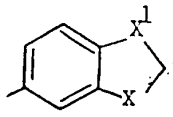
t is 0, 1 or 2;

X and X^1 are each independently O or CH_2;

s is 1, 2 or 3;

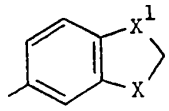
and Het^1 is pyridyl, pyrazinyl or thienyl.

2. A compound as claimed in claim 1 wherein R^1 is a group of the formula:-


or


where R^4, R^5, X and X^1 are as defined in claim 1.

3. A compound as claimed in claim 2 in which R^1 is:-



where X and X^1 are as defined in claim 1.

4. A compound as claimed in claim 3 in which X and X^1 are O.

5. A compound as claimed in any one of the preceding claims in which R^2 and R^3 are both H, m is O or 1, n is 1 or 2, Y is a direct link, and the sum of p, q and r is 3 or 4.

6. A compound as claimed in any one of the preceding claims in which, when the group "Het" is represented by formula (A), then:-

(i) p is O, q is 2 and r is 1,

(ii) p is 1, q is 1 and r is 1,

(iii) p is 1, q is 2 and r is 1,

or (iv) p is 2, q is 2 and r is O.

7. 7-anti-(Diphenylmethoxymethyl)-2-(3,4-methylenedioxyphenethyl)-2-azabicyclo[2.2.1]heptane.

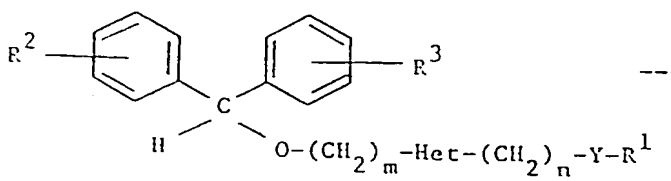
8. A pharmaceutical composition comprising a compound of the formula (IA) or (IB) as claimed in any one of the preceding claims, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable diluent or carrier.

9. A compound of the formula (IA) or (IB) as claimed in any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, for use as a medicament.

10. The use of a compound of the formula (IA) or (IB) as claimed in any one of claims 1 to 7, or of a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating irritable bowel syndrome.

11. A method of treating irritable bowel syndrome in a patient in need of such treatment, which comprises administering to said patient an effective amount of a compound of the formula (IA) or (IB) as claimed in any one of claims 1 to 7, or of a pharmaceutically salt thereof.

12. A process for preparing a compound of the formula (IA) or a pharmaceutically acceptable salt thereof:-



--- (IA)

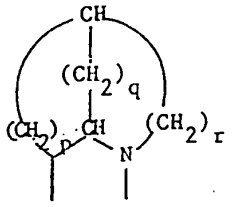
where R^2 and R^3 are each independently H, halo or C_1-C_4 alkyl;

m is 0, 1 or 2;

n is 1, 2 or 3;

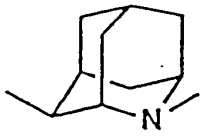
Y is a direct link, O or S; with the proviso that when n is 1, Y is a direct link;

Het is a group of the formula:-



(A)

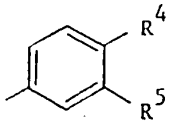
or

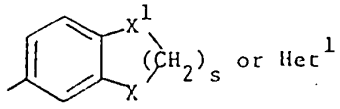


(B)

where p is 0, 1 or 2, q is 1, 2 or 3, and r is 0, 1, 2 or 3, with the proviso that the sum of p, q and r is at least 3, the N atom of "Het" being attached to the group $(CH_2)_n$ in formula (IA) and to the H atom in formula (IB);

and R^1 is a group of the formula:-





where R^4 and R^5 are each independently H, C_1-C_4 alkyl, C_1-C_4 alkoxy, $-(CH_2)_tOH$, halo, trifluoromethyl, cyano, $-(CH_2)_tNR^6R^7$, $-CO(C_1$-C_4 alkyl), $-OCO(C_1$-C_4 alkyl), $-CH(OH)(C_1$-C_4 alkyl), $-C(OH)(C_1$-C_4 alkyl$)_2$, $-SO_2NH_2$, $-(CH_2)_tCONR^6R^7$ or $-(CH_2)_tCOO(C_1$-C_4 alkyl);

R^6 and R^7 are each independently H or C_1-C_4 alkyl;

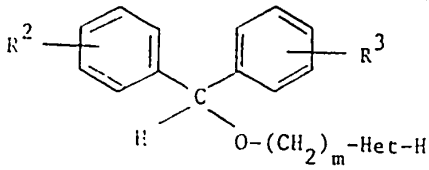
t is 0, 1 or 2;

X and X^1 are each independently O or CH_2;

s is 1, 2 or 3;

and Het^1 is pyridyl, pyrazinyl or thienyl;

characterised by reacting a compound of the formula (IB):-



--- (IB)

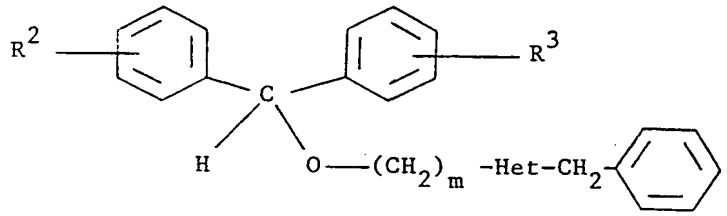
where R^2, R^3, Het and m are as defined above, with a compound of the formula (II):-

--- (II)

in which R^1, Y and n are as defined above and Q is a leaving group, followed by, optionally, conversion of the product of the formula (IA) into a pharmaceutically acceptable salt.

13. A process as claimed in claim 12, characterised in that Q is Cl, Br, I or methanesulfonyloxy, and in that the reaction is carried out in the presence of an acid acceptor.

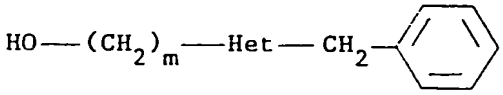
14. A process for preparing a compound of the formula (IB) as defined in claim 12, or a pharmaceutically acceptable salt thereof, characterised by the catalytic hydrogenation of a compound of the formula (IC):-



--- (IC)

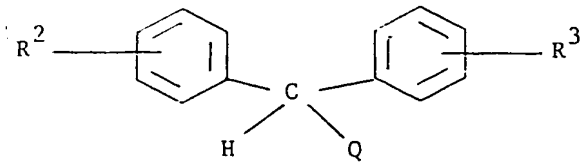
where R^2, R^3, Het and m are as defined for formula (IB), said process being followed by, optionally, conversion of the product (IB) into a pharmaceutically acceptable salt.

15. A process for preparing a compound of the formula (IC) as defined in claim 14, or a pharmaceutically acceptable salt thereof, characterised by reacting a compound of the formula:-



---(III)

where Het and m are as defined for formula (IC), with a compound of the formula:-



--- (IV)

where R^2 and R^3 are as defined for formula (IC) and Q is a leaving group, said process being followed by, optionally, conversion of the product (IC) into a pharmaceutically acceptable salt.

16. A process as claimed in claim 15, characterised in that Q is Br or OH.

17. A process for preparing a compound of the formula (IA) as defined in claim 12 in which n is 2, Y is a direct link, and R^1 is 2- or 4-pyridyl or pyrazinyl, characterised by reacting a compound of the formula (IB) as defined in claim 2 with 2- or 4- vinylpyridine or 2-vinylpyrazine.

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : C07D 405/08, 471/08, 209/52 C07D 451/02, A61K 31/435 A61K 31/46 // C07D 471/08

A3

(11) International Publication Number: WO 92/05172

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(21) International Application Number: PCT/EP91/01705

(22) International Filing Date: 9 September 1991 (09.09.91)

(30) Priority data:
9020051.0 13 September 1990 (13.09.90) GB

(71) Applicant *(for GB only)*: PFIZER LIMITED [GB/GB]; Ramsgate Road, Sandwich, Kent CT13 9NJ (GB).

(71) Applicant *(for all designated States except GB US)*: PFIZER INC. [US/US]; 235 East 42nd Street, New York, NY 10017 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)* : ALKER, David [GB/GB]; CROSS, Peter, Edward [GB/GB]; KEMP, John, Edward, Glyn [GB/GB]; Pfizer Central Research, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB).

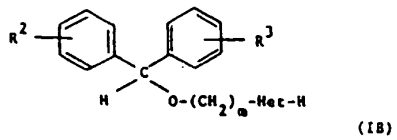
(74) Agents: WOOD, David, John et al.; Pfizer Limited, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB).

(81) Designated States: AT (European patent), BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FI, FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, LU (European patent), NL (European patent), SE (European patent), US.

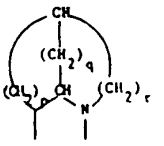
Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments

(88) Date of publication of the international search report:
29 May 1992 (29.05.92)

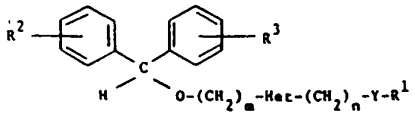
(54) Title: MUSCARINIC RECEPTOR ANTAGONISTS



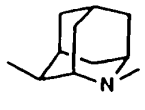
(IB)



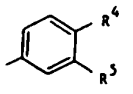
(A)



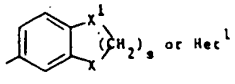
(IA)



(B)



(a)



(b)

(57) Abstract

Muscarinic receptor antagonists, useful especially in the treatment of irritable bowel syndrome, of formula (IA) or (IB) or a pharmaceutically acceptable salt thereof, where R^2 and R^3 are each independently H, halo or C_1-C_4 alkyl; m is 0, 1 or 2; n is 1, 2 or 3; Y is a direct link, O or S; with the proviso that when n is 1, Y is a direct link; Het is a group of formula (A) or (B), where p is 0, 1 or 2, q is 1, 2 or 3, and r is 0, 1, 2 or 3, with the proviso that the sum of p, q and r is at least 3, the N atom of "Het" being attached to the group $(CH_2)_n$ in formula (IA) and to the H atom in formula (IB); and R^1 is a group of formula (a), (b) or Het^1, where R^4 and R^5 are each independently H, C_1-C_4 alkyl, C_1-C_4 alkoxy, $-(CH_2)_tOH$, halo, trifluoromethyl, cyano, $-(CH_2)_tNR^6R^7$, $-CO(C_1$-C_4 alkyl), $-OCO(C_1$-C_4 alkyl), $CH(OH)(C_1$-C_4 alkyl), $-C(OH)(C_1$-C_4 alkyl)$_2$, $-SO_2NH_2$, $-(CH_2)_tCONR^6R^7$ or $-(CH_2)_tCOO(C_1$-C_4 alkyl); R^6 and R^7 are each independently H or C_1-C_4 alkyl; t is 0, 1 or 2; X and X^1 are each independently O or CH_2; s is 1, 2 or 3; and Het^1 is pyridyl, pyrazinyl or thienyl.

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DK	Denmark	MC	Monaco		

+ **Any designation of "SU" has effect in the Russian Federation. It is not yet known whether any such designation has effect in other States of the former Soviet Union.**

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
Y	Hoppe Seylers Zeitschrift für Physiologische Chemie, vol. 321, 1960, (Berlin, DE), J. BENZ et al.: "Synthesen von Scopin-benzhydryläthern", pages 148-160, see page 149, paragraph 1; page 151, compounds XV,XVI	1,10

INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 91/01705

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 C 07 D 405/08 C 07 D 471/08 C 07 D 209/52
C 07 D 451/02 A 61 K 31/435 A 61 K 31/46 //(C 07 D 471/08

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	C 07 D 405/00 C 07 D 471/00 C 07 D 209/00 C 07 D 451/00

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
Y	US,A,4721783 (W.M. DAVIS) 26 January 1988, see column 7, lines 17-35; claim 1 ---	1,10
Y	WO,A,9110651 (PFIZER) 25 July 1991, see pages 8-11; claim 1 ---	1,10
Y	WO,A,9110650 (PFIZER) 25 July 1991, see page 9, paragraph 6 - page 12; claim 1 ---	1,10
Y	Arzneimittel Forschung, vol. 14, no. 8, 1964, (Aulendorf, DE), C. VAN DER STELT et al.: "The effect of alkyl substitution in drugs. Part IX. Synthesis and properties of some trifluoromethyl-substituted benzhydryl ether derivatives", pages 964-967, see whole document --- -/-	1,10

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
18-03-1992	29. 04. 92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	Natalie Weinberg

Form PCT/ISA/210 (second sheet) (January 1985)

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. EP 9101705 SA 50744

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 09/04/92
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A- 4721783	26-01-88	US-A- 4857535	15-08-89
WO-A- 9110651	25-07-91	None	
WO-A- 9110650	25-07-91	None	

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☒ OBSERVATION WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This International search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claim numbers *** because they relate to subject matter not required to be searched by this Authority, namely:

*** Remark: Although claim 11 is directed to a method of treatment of the human/animal body the search has been carried out and based on the alleged effects of the composition

2. ☐ Claim numbers because they relate to parts of the International application that do not comply with the prescribed requirements to such an extent that no meaningful International search can be carried out, specifically:

3. ☐ Claim numbers because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this International application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International search report covers all searchable claims of the International application.

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this International search report covers only those claims of the International application for which fees were paid, specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.